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Progress in Retinal and Eye Research 25 (2006) 79–97
Progress in
RETINAL AND EYE RESEARCH
www.elsevier.com/locate/prer

The psychophysics of glaucoma: Improving the structure/function relationship

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Abstract

Perimetry of some kind remains an important tool in the detection, diagnosis and monitoring of glaucomatous damage to the visual pathway. However, recent studies have served to reinforce the suspicion that conventional perimetry does not possess the sensitivity to detect the earliest signs of functional loss resulting from glaucoma. The relationship between differential light threshold and ganglion cell loss is extremely weak and, in the early stages of glaucoma, non-existent. Alternative, more novel perimetric techniques seem to offer promise of better detectability for early loss by claiming to tap in to one or other of the separate parallel pathways of the visual system. While some of these tests show potential for better detection and monitoring of glaucoma, the reasons why this might be so are not always clearly formulated or represented. This leads to misunderstanding of what the test actually measures and of the glaucomatous disease process itself. This paper seeks to revisit and review the theory underlying psychophysical testing of visual function related to glaucoma and stresses the importance of developing tests that are based on a firm theoretical understanding of visual function and processing in order to both detect glaucoma at an earlier stage and better understand the mechanisms of loss from the disease process.

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doi:10.1016/j.preteyeres.2005.06.001

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1. Introduction

Glaucoma is an insidious condition, the second major cause of blindness globally (Kingman, 2004) and the leading cause of blindness in the developed world (Resnikoff et al., 2004; Saw et al., 2004). The condition is characterised functionally by a progressive loss of the visual field as a result of neural damage and, in primary open angle form, has a prevalence of 1.5–8.5% in people over the age of 40 years depending on the study method and ethnic group examined (Tuck and Crick, 1998; Anton et al., 2004; Iwase et al., 2004; Mitchell et al., 2004; Ntim-Amponsah et al., 2004; Varma et al., 2004; Wadhwa and Higginbotham, 2005). There are few things we can say with confidence about the glaucomatous disease process, perhaps the only one being that it results in death or dysfunction of retinal ganglion cells. The site of damage is commonly accepted to be the nerve fibres at the level of the lamina cribrosa, but the mechanisms of damage, whether by necrosis, apoptosis or some other mechanism (Osborne et al., 1999) are still poorly understood, and may be different for different types of glaucoma. An ageing population and an age-related condition mean that the morbidity associated with this condition is rising.

The detection and management of glaucoma is primarily based upon three clinical measures: the intraocular pressure, the appearance of the optic nerve head and an examination of the visual field. While impressive new techniques have been developed in recent years to examine changes in optic disc morphology, perimetric testing remains an integral and important part of clinical glaucoma examination.

Visual field tests have the advantage of actually measuring visual function, the maintenance of which is the *raison d'etre* of treatment. The early detection of glaucomatous damage and the subsequent monitoring of change remain difficult tasks for clinicians. In the last 10 years much interest, in the form of both morphological and psychophysical/perimetric studies, has been directed at the idea of early selective damage to one of the specialised 'parallel pathways' which carry information about motion or colour to higher visual centres. Whatever the mechanism, most clinicians agree that some sort of psychophysical testing will always be required to detect and diagnose the presence of glaucoma in any individual. In this paper we briefly examine what, if anything, perimetric testing has contributed to our understanding of glaucoma and discuss the prospects for developing tests which better relate structure to function in an attempt to increase detectability of glaucoma by psychophysical means.

2. Conventional perimetry

Since the discovery over a century ago of peripheral visual field defects in the course of glaucoma progression, the detection and monitoring of glaucoma has increasingly included some kind of assessment of the patient's visual field. Typically, this kind of assessment, termed perimetry, has involved the presentation of small spots of light, of different intensity, at different locations in the visual field. The patient's task is simply to indicate the presence or absence of each spot at all of the tested locations. The resultant field plot is intended to represent some kind of map of the location and severity of the damaged areas of the visual field. It is also used to determine whether or not progression is present during routine follow-up of glaucoma patients. Few would doubt the importance of such a test in the diagnosis and management of glaucoma and the last 20 years have seen much technological investment in designing and refining the perimeters used for this purpose.

The advent of computerisation has resulted in early crude manual perimeters being replaced by sleek, modern instruments in which every aspect of the stimulus is controlled by a computer. In fact most of the effort expended in perimetric design in recent years has been on the software front. There are good reasons

for this. As with any task requiring the detection of a signal in noise, perimetric thresholds display significant variability. This variability can originate in the stimulus or the observer. Computerisation has succeeded not only in reducing some of the variability owing to poor stimulus control and different operators, but the resultant data are subsequently analysed to yield values for false positive responses, false negative responses, fixation losses, mean defect (MD), pattern standard deviation (PSD), corrected pattern standard deviation (CPSD), total defect (TD) and hemifield analysis (Wild, 1988). Nevertheless, significant variability remains.

Another reason often cited for variability is the length of time taken to assess the glaucomatous visual field. The terms Swedish Interactive Thresholding Algorithm (SITA) and SITA Fast are well known to users of Humphrey perimeters as software packages which significantly reduce testing time without (it is claimed by some) reduction in the sensitivity or specificity of the test. These items of software have not only helped reduce variability as a result of patient fatigue but, some would claim, represent a more reliable psychophysical paradigm to measure localised threshold. However, this paper is not so much concerned with *how* threshold is measured as *what* threshold is measured, and its appropriateness for the task of detecting glaucomatous loss.

The form of perimetry discussed here, where the subject is presented with a small spot of white light on a white background is usually termed "conventional perimetry" or "white-on-white perimetry". Despite modern sophisticated attempts to control patient and stimulus variability, the basic question asked of the patient remains unchanged for decades, namely, "Did a spot of light just come on or not?"

2.1. Limitations of conventional perimetry: the structure/function relationship

Conventional perimetry has suffered criticism in more recent times as a result of several studies that have graphically demonstrated its shortcomings. The studies of Quigley et al. (1982, 1989) were among the first to suggest that large numbers of optic nerve fibres could be lost before a significant defect could be demonstrated by conventional perimetry. Although these findings were hotly debated and criticised, subsequent studies seem to have born out Quigley's assertions (Harwerth et al., 1999; Kerrigan-Baumrind et al., 2000). The study of Harwerth et al. (1999), conducted on primates, seemed to indicate that the relationship between differential light sensitivity (DLS, in dB) and ganglion cell loss (in %) was curvilinear and, for field losses up to 15 dB or ganglion cells losses up to 60%, there was no relationship between the two measurements (Fig. 1a). The results suggested that there existed an enormous reserve in the ganglion cell population and, at the same time, the possibility that significant threshold elevations could occur prior to any ganglion cell loss. Initial alarm at these findings was tempered by the observation that, when considering the underlying number of ganglion cells, a linear 1/Lambert scale for DLS is more appropriate (Garway-Heath et al., 2000). A linear relationship between the two values was found when Harwerth et al. (2002) later plotted their same data on a log-log scale: a ganglion cell reserve was also no longer apparent (Fig. 1b). In a later study, Garway-Heath et al. (2002) measured light sensitivity and temporal neuroretinal rim area in normals and glaucoma patients and indicated that the curvilinear relationship between DLS and ganglion cell loss, which they felt disproportionately emphasised advanced loss at the expense of early loss, became linear if DLS was plotted in a 1/Lambert scale instead of a dB scale (Fig. 1c). Nevertheless, examination of the error bars in the revised plot of Harwerth et al. (Fig. 1b) reveals enormous variability consistently all the way up the scale from normal to advanced glaucoma.

Of course the source of the variability does not all lie at the door of perimetry; the reliability of anatomical counts of ganglion cells is not without error, not least because of the presence of displaced amacrine cells in the ganglion cell layer, the proportion of which increases with eccentricity. However, the enormous scatter within both the normal and glaucomatous subjects in the plot of Garway-Heath et al. (Fig. 1c) suggests that, rather than some glaucoma subjects displaying visual field defects prior to ganglion cell drop-out as suggested by Harwerth et al., the basic problem is that the fundamental relationship between the two measures is extremely weak. A more recent study by Harwerth et al. (2004), again using primates with experimentally induced glaucoma, found that the relationship strengthened significantly when retinal eccentricity was taken into account. However, this and the previous study used subjects where glaucomatous damaged ranged from mild to very advanced. There may be a significant correlation between the two measures using such a wide range of field loss, but this is hardly surprising. Why should we base our diagnosis on a test that can only relate ganglion cell number to visual field sensitivity when the subjects range from normal to seriously impaired? If we are concerned about detecting early glaucomatous damage or small changes in sensitivity it is clear that at the bottom (less advanced loss) end of the plot any relationship between the two measures is non-existent. What would be more interesting would be a test that could demonstrate a significant relationship between psychophysical threshold and ganglion cell density in *early* glaucoma or, more impressively, in normal subjects who we know display significant inter-individual variation in ganglion cell numbers (Curcio

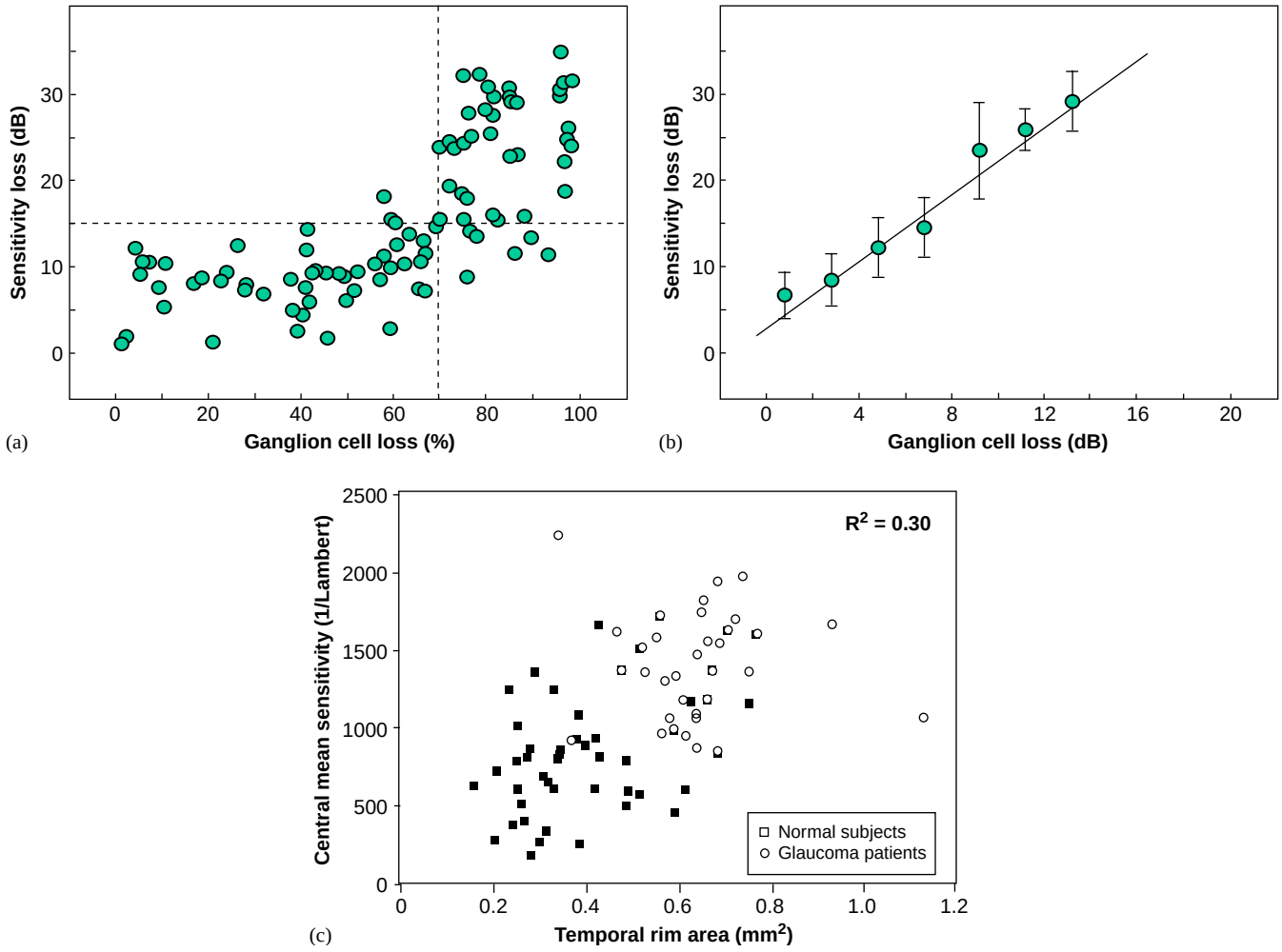

Fig. 1. (a) The relationship between conventional perimetric threshold in dB and ganglion cell density is curvilinear and at first glance indicates enormous reserve below 15 dB loss (after Harwerth et al., 1999). (b) While this relationship becomes linear when plotted on a log–log scale (after Harwerth et al., 2002), and (c) the relationship between threshold and neural rim area is also linear when threshold is plotted on a 1/Lambert scale (after Garway-Heath et al., 2002), it should be noted that enormous scatter remains, even at the normal end of the curve, and a significant relationship between conventional perimetric threshold and ganglion cell loss exists only because subjects with a wide range of glaucomatous damage are included.

and Allen, 1990). Harper et al. (2000) pointed out that, in appraising the diagnostic accuracy of a clinical test, it is important to consider the extent to which the study population is representative of the population in which the test is designed for use. In this regard, studies which demonstrate a strong correlation between psychophysical threshold and ganglion cell loss in a population ranging from normal to end-stage glaucoma are of little value. The ability to detect subtle early damage is the important thing.

Furthermore, the low level of repeatability demonstrated by conventional perimetry in turn leads to the inability to reliably identify visual field progression. Recent studies have examined the ability of conventional perimetry to detect glaucomatous progression based on different combinations of defect classification, trend analysis and event analysis (Katz, 1999; Vesti et al., 2003; Boden et al., 2004; Nouri-Mahdavi et al., 2004). Different analysis methods may display distinct advantages and disadvantages in different circumstances but none seems to be universally ideal (Spry and Johnson, 2002), the hope usually being that some new improved method of analysis will become available in the future. However, the recent study of longitudinal visual field change in glaucoma by Artes and Chauhan (2005) which again found a poor relationship between conventional perimetry and optic disc change and concluded that the two indicators provide largely independent measures of progression.

2.2. Historical baggage

While the relationship between structure and function is weak for conventional perimetry, this does not mean

there is not room for improvement in the ability of perimetry to detect early functional change in glaucoma. One factor, which perhaps requires careful re-examination is stimulus size. The stimulus sizes employed by conventional static perimetry and SWAP have been imported without modification from Goldmann kinetic perimetry, including the nomenclature. The most typically used stimulus size in conventional white-on-white perimetry is the Goldmann size III. Typically, this size is used across the entire visual field. While some older static perimeters employed increasing stimulus size with increasing eccentricity in an attempt to match stimulus size to increasing receptive field size, this idea has been ignored in recent years. What stimulus size is most appropriate, and under what conditions?

Other considerations include stimulus distribution, background illumination and refractive error, which we shall discuss later.

3. Selective vs. non-selective loss in glaucoma: short wavelength automated perimetry

Short Wavelength Automated Perimetry (known as SWAP) was developed following reports that patients with early glaucoma often displayed short wavelength colour vision defects (King-Smith et al., 1984; Heron et al., 1987, 1988). The short-wavelength sensitive (SWS) pathway is mediated by the small bistratified ganglion cells which synapse at two levels in the inner plexiform layer and project to the koniocellular layers of the lateral geniculate nucleus (Martin et al., 1997). These cells, termed blue-ON, which constitute between 1% and 7% of the total ganglion cell population depending on eccentricity (Dacey, 1994) receive their excitatory input from the blue cones through the S-cone bipolar cell, and their inhibitory input from a combination of the red and green cone signal through off-bipolars. The existence of a blue-OFF pathway remains a subject of debate but recent psychophysical evidence is beginning to provide more support (Shinomori et al., 1999; McLellan and Eskew, 2000; Vassilev et al., 2000, 2003).

SWAP employs Stiles' two-colour threshold method, which adapts out the long and medium wavelength sensitive pathways using a bright broadband yellow background and then tests the SWS pathway using a narrow band blue stimulus. Much evidence has accrued to indicate that SWAP is indeed capable of detecting glaucoma at an earlier stage that white-on-white perimetry, at least in many cases (Sample et al., 1988; Sample and Weinreb, 1990; Sample and Weinreb, 1992; Casson et al., 1993; Johnson et al., 1993a, b, 1995; Johnson, 1996; Spry et al., 2005). That this is because of selective damage to the SWS pathway has been challenged by alternative theories, one of which is the 'reduced redundancy' hypothesis (Johnson, 1994).

3.1. The 'reduced redundancy' hypothesis

The 'reduced redundancy' hypothesis (Johnson, 1994) proposed that short wavelength sensitivity (SWS) loss appears to precede achromatic loss, not because the short wavelength sensitive pathway is more vulnerable than any other but because, in isolation, it is sparse and lacks the 'back-up' coverage of the other ganglion cell mosaics. Under the conditions of standard perimetry, a white stimulus should be detectable by all sub-systems in the retina, the ganglion cell receptive fields of which overlie each other. If a few cells, of whatever class, become dysfunctional, the stimulus can still be detected by functional cells of a different type, which 'fill the gap'. This applies equally to any cell type and only when all cells covered by the stimulus become dysfunctional does it become undetectable. The SWAP stimulus, it is proposed, detects damage earlier because the stimulus is only detectable by the sparse small bistratified ganglion cell mosaic, without the redundancy afforded by the other cell types. This was an insightful and credible hypothesis that received widespread interest in the perimetry world.

Calculations of responding cell numbers underlying white-on-white and SWAP stimuli would seem to support the hypothesis. From anatomical counts of ganglion cell density across the human retina (Curcio and Allen, 1990), excluding the nasal meridian, a Goldmann III target covers around 260 ganglion cells of all types at 5° eccentricity and 12 cells at 25°. On the other hand, from morphological estimates of small bistratified ganglion cell density (Dacey, 1994) a Goldmann V target (with an angular subtense of 1.72°) covers approximately 50 small bistratified ganglion cells at 5° eccentricity but only 7 cells at 25°. However, when predicting 'redundancy', it is not necessarily the total *number* of cells underlying the stimulus that is the most important factor. Pearson et al. (2001) found glaucomatous defects of similar magnitude for blue-on-white and red-on-white stimuli (designed to isolate the blue-ON and red/green chromatic mechanisms) even though the number of cells covered was five times higher for the red stimuli than the blue. Clearly, the number of cells underlying the stimulus *in normals* is not the only consideration.

3.2. The dendritic field

The term 'coverage' is used to describe the relationship between density and dendritic field overlap. Coverage is calculated as the product of cell density (in ganglion cells/mm^2) and dendritic field area (in mm^2). Thus, a coverage of 1 indicates 'tiling' or abutting dendritic fields; anything greater than 1 indicates overlapping fields and anything less than 1 means incomplete coverage. Ganglion cell mosaics with lower coverage

factors could logically be expected to display 'holes' prior to those with higher coverage factors (Maddess and Henry, 1992; Maddess et al., 1999). Dacey (1993a, b, 1994) provides the most up-to-date information we have about the coverage patterns of different classes of ganglion cells, in particular the small bistratified cells. Parasol (magnocellular) ganglion cells stratify near the centre of the inner plexiform layer and display a coverage factor of around 3.5 (significant overlap). Small bistratified cells are low in number, stratify at both the inner and outer margins of the outer plexiform layer and have dendritic fields that display similar coverage (3) and overlie those of the parasol cells. The midget cells are greatest in number but have dendritic fields that, while overlapping those of the other cell types, display coverage of no more than 1 themselves. If low coverage results in holes in the ganglion cell array at an earlier stage in glaucoma, a stimulus that isolates midget cells should result in a greater ability to detect glaucomatous damage. This was not born out by the study of Pearson et al. (2001) mentioned above. Clearly, coverage factor is not the only consideration either in determining sensitivity to glaucomatous damage.

3.3. The receptive/perceptive field and Ricco's area

With any of the different ganglion cell mediated channels, the dendritic field and receptive field are not the same. The red and green cones converge on midget cells via smaller numbers of both ON and OFF bipolar cells, resulting in concentric ganglion cell receptive field organisation with either ON or OFF centres and surrounds. Thus, the retinal area of influence of the average midget cell extends well beyond its dendritic tree, particularly in the peripheral retina. In contrast, the sparse blue cones, while similar in number to the small bistratified ganglion cells which they serve, typically each connect to two s-cone bipolars which in turn connect to two small bistratified ganglion cells (Calkins, 2001). While the small bistratified ganglion cells do not display concentric ON and OFF receptive field organisation, with each S-cone connecting to numerous ganglion cells their representation is increased and the overlap of small bistratified ganglion cell receptive fields is likely to be very high. However, Chichilnisky and Baylor (1999) point out that, while a particular S-cone may connect with numerous surrounding ganglion cells, it provides the dominant input to only one ganglion cell. Thus, the functional redundancy of such a system may not be as high as the anatomy might predict, particularly if the psychophysical task is one of contrast detection.

However, it is strictly not either the morphological dendritic field or the physiological receptive field that determines redundancy, but their psychophysical correlate the *perceptive* field in particular the area of complete spatial summation, or Ricco's area. Within Ricco's area, the product of stimulus area and threshold contrast is constant. As stimulus size increases beyond this critical area, the reciprocal relationship between threshold and area begins to break down and the level of summation is somewhat less, obeying Piper's law, and beyond this the system eventually displays probability summation only. Under the latter conditions any individual ganglion cell within such an area will contribute little to the overall threshold response in a normal eye. The neurological basis of Ricco's area has been attributed to the degree of overlap of ganglion cell receptive fields (Fisher, 1973; Lie, 1980), the receptive field centre size (Glezer, 1965; Inui et al., 1981) or summation at some higher visual area (Richards, 1967).

Classic experiments have measured Ricco's area under photopic conditions in normal eyes and found it to be about 8 min of arc at 5° eccentricity and about 16 min of arc at 25° eccentricity (Wilson, 1970) (see Fig. 2). This means that, in a normal functioning system, a Goldmann III target (at 26 min of arc diameter) is about the same size as Ricco's area at 40°, about 2.5 times Ricco's area at 25° eccentricity, but about 13 times Ricco's area at 5°. This would mean that, in a normal eye, stimulus detection in conventional perimetry is determined in both the central and peripheral parts of the field by probability summation in that the stimulus is much larger than Ricco's area and covers many ganglion cell receptive fields. However, this assumes a normally functioning visual system.

Ricco's area has been shown to increase in size with age, at least for scotopic stimuli (Schefrin et al., 1998). This finding has been explained as a reassignment of

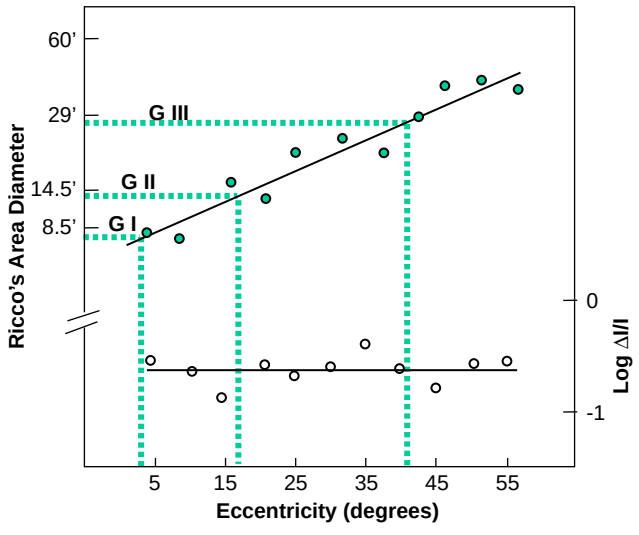

Fig. 2. Ricco's area vs. eccentricity for achromatic stimuli (after Wilson, 1970). Dotted lines indicate the eccentricity at which different Goldmann targets become of similar size to Ricco's area. Lower plot indicates constancy of $\Delta I/I$ for stimuli the size of the localised Ricco's Area.

ganglion cell inputs between higher visual neurons as a compensation for the loss of ganglion cells with age, resulting in an areal increase in cortical receptive field size. Ricco's area may also change in size with glaucoma. Fellman et al. (1989) measured white-on-white perimetric thresholds for size III and V Goldmann targets at different eccentricities in normal and glaucomatous eyes. They concluded that increasing stimulus size improved retinal sensitivity more than increasing contrast in glaucoma patients: the opposite was true in normals, indicating that the area of spatial summation is different in glaucoma. They found that increased sensitivity for the larger target could be explained most of the time either by the 'recruitment' of nearby nearly normal areas or by normal spatial summation. In 27% of patients however, a level of summation over and above expected physiological levels ('pathological' summation) was demonstrated.

While Ricco's area itself was not directly measured in that study, nevertheless, in glaucoma, while threshold in the more peripheral field (25°) may initially be determined by probability summation in that the stimulus size is somewhat larger than Ricco's area, as cells progressively become dysfunctional, enlargement of Ricco's area would mean that it soon becomes the same size as the stimulus and threshold thus becomes determined by spatial rather than probability summation. At this point any further loss of cells should be much more detectable—unlike the central retina where Ricco's area is very small and remains covered many times over by the stimulus well into the advanced disease stage. For this reason, glaucoma may appear to damage more peripheral locations first.

Pooling by second-stage spatial filters has been suggested as a means to linearise the relationship between perimetric threshold and ganglion cell number for both normal and pathological fields (Swanson et al., 2004). In that study a two-parameter spatial summation function was used to fit data relating perimetric sensitivity (in dB) with log ganglion cell number under a Goldmann III target. The authors found the function to be consistent with the critical summation area increasing in size to compensate for decreasing ganglion cell density. At more peripheral locations sensitivity was linearly related to ganglion cell number. This is in many ways similar to the concept of Ricco's area which has previously been suggested as a mechanism by which a constant number of ganglion cells is contained within the area of complete spatial summation for both achromatic (Glezer, 1965) and chromatic stimuli (Vassilev et al., 2005).

3.4. Ricco's area for SWS stimuli

Volbrecht et al. (2000) demonstrated that Ricco's area of complete spatial summation for SWS isolating stimuli is somewhat larger than the small bistratified ganglion cell dendritic field, especially outside the fovea and increases in monotonic fashion with eccentricity. More recently Vassilev et al. (2003, 2005) found that Ricco's area for SWS stimuli, was consistently 1.6–1.8 times the size of the small bistratified dendritic tree and constantly contained about 3–4 cells beyond 10° with no definite signs of eccentricity dependence. With such significant overlap we could reasonably expect the redundancy to be fairly high in such a system. We previously calculated that a Goldmann V target (with an angular subtense of 122 min of arc) as used in SWAP, covers approximately 90 small bistratified ganglion cells at 5° eccentricity but only 12 cells at 25°. These numbers represent hugely more than the number of cells calculated to underlie Ricco's area at 5°, but at 25° where the area of complete summation for S-cone stimuli has been found to constantly cover 3–4 cells (Vassilev et al., 2003), threshold will display a larger coefficient of summation and, as such, may display less 'redundancy' and greater sensitivity to damage by glaucoma.

Pearson et al. (2001) speculated that greater pooling of ganglion cell responses by chromatic mechanisms at a *cortical* level results in a greater number of chromatic cortical neurons displaying reduced responses to punctate ganglion cell loss; probability summation across cortical neurons sampling from the same retinal area in turn results in greater reduction in chromatic thresholds. This may be the case, but it may also be that Ricco's area changes disproportionately for different pathways in glaucoma. To date this has not been examined.

4. Background luminance

As with stimulus size, the background luminance of many static perimeters, including the Humphrey instruments, is imported from Goldmann kinetic perimetry (31.5 apostilbs). This background level was specifically chosen by Goldmann for his kinetic perimeter because it places the average normal subject in the range where $\delta I/I$ becomes constant (Glezer, 1965) and Weber's law is said to operate. Under such conditions small changes in retinal illumination, as a result of pupil size or instrument voltage variation, do not affect stimulus visibility. In reality, 31.5 apostilbs represents the highest practical artificial illumination level (in terms of dymanic range) available at the time Goldmann designed his perimeter (Anderson and Patella, 1999). It was, however, incorporated unquestioningly into many of the later static perimeters. The relative advantages and disadvantages of different background illumination levels in terms of dynamic range have been discussed before (Wild, 1988). However, Glezer showed as early as 1965 (Glezer, 1965) that Ricco's area of complete spatial

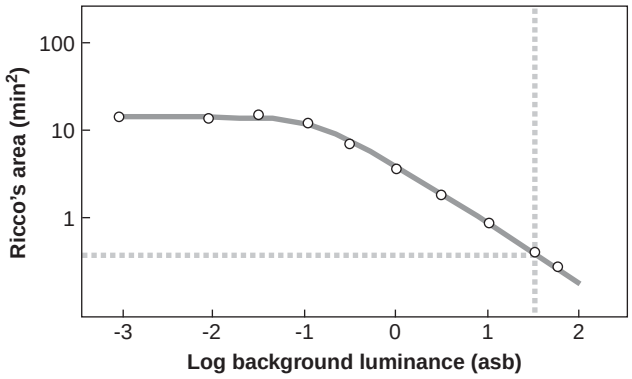

Fig. 3. Variation in the size of Ricco's area with background illumination in the fovea (after Glezer, 1965).

summation decreases as the square root of the increase in background illumination in the fovea (Fig. 3). The study of Fellman et al. (1989) found an improvement in sensitivity with decreasing background luminance for a Goldmann III stimulus in both glaucoma patients and normal subjects. Interestingly, this improvement was larger in normals than glaucoma patients, especially at larger eccentricities.

Thus a lower background illumination level may result in a larger Ricco's area and potentially earlier detection of sensitivity loss through spatial summation mechanisms.

It may be that stimuli scaled to the size of Ricco's area for each *retinal pathway*, *background luminance* and *eccentricity* are most appropriate to detect drop-out by small numbers of ganglion cells. Little effort has been expended in determining optimal stimulus sizes for screening or monitoring, or how Ricco's area changes with different degrees of damage across the same field. It may be appropriate to employ stimulus sizes that start small and change locally with defect depth as the area of complete summation changes at different field locations. Without such work, conventional perimetry will continue to have difficulty in detecting early losses of retinal ganglion cell function.

5. Stimulus distribution

The most commonly utilised forms of conventional perimetry employ stimulus patterns that are uniform in spatial distribution. Concern has been expressed recently that this may not be appropriate since such a pattern does not accurately mirror the distribution of retinal ganglion cells, which are much more numerous in the central retina and decline in density with eccentricity. It has been postulated that this is one reason why the central visual field rarely displays visual field defects until the glaucoma disease process is well advanced; if ganglion cell density is greater centrally, any scotomata will be more localised and require more localised testing.

Dacey's data on the relative distributions of different ganglion cell classes across the retina were based on dendritic field diameter and the assumption that coverage does not change with eccentricity. However, parasol coverage was only examined from 10° eccentricity (3 mm) to the far periphery. Constant coverage was *assumed* for the midget and small bistratified mosaics but not verified. This may not be the case. If the central field, with its greater ganglion cell density, also possesses greater receptive field overlap and hence greater redundancy, increasing stimulus density may not automatically result in a significantly increased ability to localise defects. Nevertheless, examination of the central field with a higher density stimulus array does indeed appear to find scotomata that previously went undetected (Westcott et al., 1997).

6. Peripheral refractive error

Unfortunately, conventional perimetric stimuli suffer from the effects of optical defocus, and smaller stimuli are more vulnerable to the low-pass filtering effects of optical blur. However, even with careful correction of foveal refractive error, eccentrically presented stimuli will suffer at the hands of off-axis refractive error, which increases with eccentricity and can be very significant, particularly in its astigmatic component (Ferree et al., 1931; Rempt et al., 1971; Lotmar and Lotmar, 1974; Millodot and Lamont, 1974; Millodot et al., 1975; Charman, 1983; Anderson et al., 2001). Many eyes also become more hyperopic or myopic in the periphery (Millodot, 1981; Charman, 1983), meaning that correcting the foveal refractive error may in some cases make the peripheral refractive error worse. It is perhaps odd that, in conducting perimetry, we carefully correct foveal refractive error and then test everywhere in the visual field except the fovea! Off-axis refractive error is usually forgotten by perimetrists and, while impossible to correct at every location at once, the use of larger stimuli, containing lower spatial frequency components may be more robust to the effects of defocus and help to minimise its effects (Anderson et al., 2001). However, there is a trade-off with the use of larger stimuli, indicated above; stimuli that are significantly larger than Ricco's area may result in thresholds being determined by probability rather than spatial summation for a longer period of the early disease process and result in poorer sensitivity to damage.

Smaller pupil sizes would also help to minimise the effects of peripheral refractive error but this of course leads to additional considerations for the perimetrist.

7. Selective vs. non-selective loss in glaucoma: the magno-parvo debate

The findings of Quigley et al. (1987) that glaucoma sufferers appeared to have fewer large optic nerve fibres was regarded by many as evidence for a selective loss of the larger magnocellular (M) ganglion cells which project to layers 1 and 2 of the lateral geniculate nucleus. Others refuted the idea of selective vulnerability, instead purporting that the apparent absence of large fibres in glaucoma patients is purely a result of shrinkage of the entire cell population (Morgan, 1994; Osborne et al., 1999) and morphological studies appear to support this claim (Morgan et al., 2000).

However, the knowledge that these cells were sensitive to high temporal frequency stimuli combined with earlier reports that glaucoma patients often displayed specific deficits in sensitivity to flickering stimuli (Tyler, 1981) resulted in many studies which sought to design tests for glaucoma which employed stimuli that moved or flickered in some way at high temporal frequency in an attempt to 'isolate' the magnocellular pathway.

7.1. Motion perimetry

Studies employing Temporal Modulation (Flicker) Perimetry (Lachenmayr et al., 1991; Casson et al., 1993; Austin et al., 1994; Yoshiyama and Johnson, 1997; Spry et al., 2005), Motion displacement perimetry (Fitzke et al., 1986; Westcott et al., 1998; Baez et al., 1995) and motion perception thresholds in both the fovea (Silverman et al., 1990; Bullimore et al., 1993; Trick et al., 1995) and periphery (Bosworth et al., 1996, 1997; Wall et al., 1997) have indicated that glaucoma patients display significant deficits in sensitivity to either flickering or moving stimuli, but studies directly comparing glaucomatous sensitivity loss with motion perimetry and conventional perimetry have not always found a selective loss for moving stimuli (Johnson, 1994; Sample et al., 1994, 2000; Graham et al., 1996; Swindale et al., 1996).

Frequency Doubling Perimetry (Johnson and Samuels, 1997) (presently commercially available as the Humphrey Matrix perimeter) purported to go further and to tap into a specific subset of magnocellular ganglion cells, the M_y cells, which display non-linear responses to increasing temporal frequency that can result in the perception of a 'frequency doubling' phenomenon (Kelly, 1966, 1981) for a sinusoidal grating flickering at high temporal frequencies. This test typically employs a low spatial frequency (0.25 c/deg) grating which counterphases at 25 Hz, making it robust to the low-pass filtering effects of optical defocus (Anderson and Johnson, 2003). It has often been reported to demonstrate sensitivity loss prior to conventional perimetry (Sample et al., 2000; Medeiros et al., 2004) although a recent study found the ability of both conventional and Frequency Doubling perimetry to detect progression little different (Haymes et al., 2005).

7.2. Isolating the M pathway?

While it is commonly acknowledged that the M pathway responds well to stimuli of low spatial and high temporal frequency (Hicks et al., 1983; Derrington and Lennie, 1984), Merigan and Maunsell (1993) point out that its response characteristics are not so different from the P cell pathway, displaying only 15% difference in peak temporal frequency, cut-off temporal frequency and peak spatial frequency. In addition, while the M pathway cells respond to lower luminance levels (Purpura et al., 1990), P cells are also perfectly capable of responding at rod mediated light levels (Virsu and Lee, 1983). Thus, there is a substantial overlap in the functional characteristics of these two pathways and most differences seem to be quantitative rather than qualitative; significant differences exist only in colour opponency, time course of response and contrast gain (Merigan and Maunsell, 1993). Other authors have also noted this when considering selective testing for glaucoma (Ansari et al., 2002a, b) and a recent study by the same group, examining contrast sensitivity for stimuli of varying spatial and temporal frequencies in glaucoma patients, found no significant differences in sensitivity loss for stimuli of low spatial and high temporal frequency (Ansari et al., 2002a, b). This being the case, how can we be certain that Frequency Doubling Perimetry thresholds are in fact mediated by the magnocellular pathway, especially since the patient is never actually asked if he/she perceives any kind of doubling illusion?! White et al. (2002) found no evidence of separate non-linear M_y cells in macaque LGN and that the spatial frequency doubling illusion was present even at quite low temporal frequencies, but not as a result of non-linearity in ganglion cell responses. They instead postulated that a loss of temporal phase discrimination in the cortex may be the underlying cause of the frequency-doubling illusion.

In the debate over the role of the M pathway, it has been suggested that M cells play very little part in perception at all (Lennie, 1980). Evidence for this comes from the observations that they are capable of responding to stimuli which modulate at temporal frequencies higher than can actually be perceived (Lee et al., 1990) and display a dominant role in contrast adaptation at a retinal level (Solomon et al., 2004). At the other extreme, how can we be sure that conventional white-on-white perimetry, with its low background luminance level, short stimulus presentation times and low contrast levels is not actually dominated by the magnocellular system? Perhaps in between these views, Drasdo (1989)

suggested that "The magnocellular and parvocellular processing streams will not usually operate in isolation (DeYeo and Van Essen, 1988; Zeki and Shipp, 1988)(sic) and a division of labour may occur depending on the stimulus."

Further evidence for the overlap in functional characteristics of the two systems and the problems associated with psychophysically isolating the magnocellular pathway is presented later. But for now, back to basics and visual acuity.

8. Improving the structure/function relationship: peripheral acuity

It has long been known that visual acuity is not as well developed in the periphery as in the fovea but among the first to measure peripheral acuity was Wertheim in 1894 (Wertheim, 1980). Wertheim required subjects to identify the orientation of a wire grid out to 70° eccentricity and found that visual acuity decreased from the fovea to the periphery in a curvilinear fashion (when plotted on linear scales). The rate of decline varied with the retinal meridian under examination. Acuity at any eccentricity was generally better in the nasal than the temporal retina, and in the superior than inferior retina. Wertheim's results have subsequently been confirmed many times and many studies have examined how peripheral acuity varies with meridian and eccentricity and the possible reasons why this is so.

However, in the past different studies employed different methods and tasks to measure grating 'acuity'. Some employed *detection* tasks where the subject was required to indicate whether or not the stimulus was present: others employed *resolution* tasks where it was necessary to indicate the orientation of the stimulus. In foveal vision these two methods yielded essentially the same answer but it became apparent that, in the periphery, detection performance often far exceeded resolution performance, even for a grating which had the same mean luminance as the surround (Thibos et al., 1987b), indicating that it was possible for a subject to detect grating contrast but remain unable to resolve the orientation. This idea may seem strange to some readers who are familiar with observing only foveal gratings where, having detected contrast, one is simultaneously able to report the orientation. However, peripheral vision differs from foveal vision in several important ways and is limited by different factors. We shall briefly examine some of these.

8.1. Optical quality

The initial stages of visual processing can be divided into two main parts. The first is the formation of the optical image on the retina. To result in good acuity, this continuous optical image must be well focused and of high quality. Optical defocus and other higher-order aberrations result in lower image quality and attenuate high spatial frequencies more than low spatial frequencies (low-pass filtering). Defocus is easily corrected with spectacle lenses but only one location at a time. The image quality of the eye is described by the modulation transfer function (MTF), which describes how much contrast is transmitted from the object to the image at different spatial frequencies. Campbell and Green (1965) calculated the eye's optical MTF by measuring contrast sensitivity under natural viewing conditions and with an interferometer, which is not affected by the diffraction and defocus effects of the eye's optics. Comparison of the two measurements yields an estimation of the amount of contrast lost during natural viewing and hence the MTF can be calculated. Their results indicated that the optical quality of the eye was better than previously reported. For pupil diameters of 2.5 mm or less the central optical quality of the eye is close to being diffraction limited, but with larger pupils ocular aberrations reduce image quality. Campbell and Gubisch (1966) confirmed that the central optics of the eye permit spatial frequencies up to 50 cycles/deg to reach the retina.

However, optical quality deteriorates towards the periphery. In addition, the focusing properties of the eye change with eccentricity. This is caused by a couple of factors, previously mentioned. Firstly, an increase in *oblique incidence astigmatism* and secondly a change in *distance of the retinal image plane* as eccentricity increases (Ferree et al., 1931; Rempt et al., 1971; Lotmar and Lotmar, 1974; Millodot and Lamont, 1974; Millodot, 1981). The optics are therefore one potentially limiting factor for visual acuity across the retina but, before discussing how optics affect visual performance we must first examine another factor which may also affect acuity.

8.2. Retinal anatomy

Attempts have also been made to provide an anatomical explanation for the observed changes in visual acuity with eccentricity. As early as 1958, Bergmann (1858) proposed a connection between acuity and spatial sampling by the cone mosaic at the fovea, and idea also advocated by Helmholtz (1925). However, following on the observations of Wertheim, Ludvigh (1941) and Polyak (1941) plotted visual acuity with cone density, showing both to decrease towards the peripheral retina, thus proposing a connection between visual acuity and the sampling properties of the retina. In 1946, Ten Doesschate (1946) introduced the concept of receptive 'units' rather than cones, connected to optic fibres. Weymouth (1958) also proposed that it is the

optic nerve fibre, or more specifically its cell of origin, the ganglion cell, that is the receptive unit and thus relevant to the peripheral minimum angle of resolution (MAR).

8.3. Optics, sampling and aliasing: a closer look

The work of Campbell and Gubisch (1966) indicated that, under normal viewing conditions, patterns beyond the neural resolution limit of the fovea are eliminated by the filtering properties of the eye's optical system. The optics, in effect, act as a low-pass filter, removing these high-frequency object components meaning they do not appear in the retinal image (Fig. 4b). This means that the optics of the eye are the limiting factor or 'weak link in the chain' for normal foveal acuity. If a grating with the same mean luminance as its surround is increased in spatial frequency it is quickly filtered out by the optics of the eye and vanishes in the fovea. As we move peripherally however, evidence exists that the neural resolution limit across the retina (Green, 1970; Curcio and Allen, 1990; Dacey, 1993b) falls off faster than optical quality (Millodot et al., 1975; Jennings and Charman, 1978, 1981; Williams et al., 1996) indicating that peripheral resolution is not limited by optics but by neural sampling. Thibos et al. (1987a) conclude that, whereas central resolution (for high contrast stimuli) is limited by optical filtering, peripheral pattern resolution is limited by 'the spacing of the receptive fields of the coarsest array of the sequence, the ganglion cells'. Evidence that peripheral resolution acuity is sampling limited comes from the ability to perceive *aliasing* (Williams, 1985; Smith and Cass, 1987; Thibos et al., 1987b; Anderson and Hess, 1990; Williams et al., 1996) when high spatial frequency grating stimuli are presented in the peripheral field. What is aliasing and how does it arise?

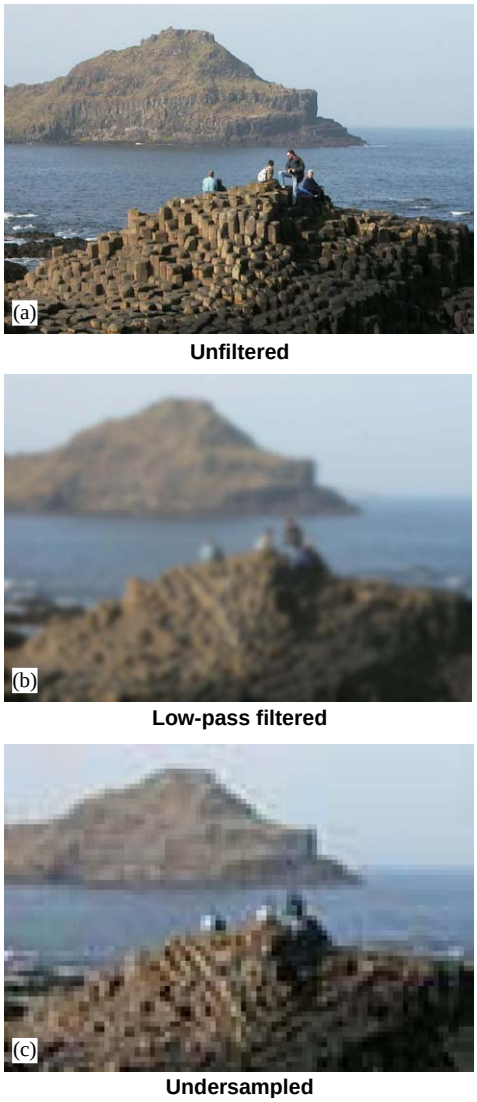

Fig. 4. (a) The hexagonally packed stones of the Giant's Causeway, County Antrim (unfiltered). (b) The same picture as it appears foveally after low-pass filtering by the eye's optics. (c) Appearance after undersampling as in the peripheral retina; note presence of aliased higher frequencies.

As previously mentioned, the spacing of the receptive fields limits the fineness of the pattern that can be resolved. According to Shannon's sampling theorem (Shannon, 1949) a sinusoidal grating must be sampled more than twice per cycle in order to be correctly (veridically) represented in terms of spatial frequency and orientation. If sampled at a lower density than this, the grating is said to be undersampled. The highest frequency that can be correctly represented by a given sampling array is called the *Nyquist* frequency. When a stimulus of high frequency is undersampled by the retinal sampling array it is commonly perceived as a pattern of lower spatial frequency and often different (non-veridical) orientation (see Fig. 4c). This phenomenon is termed aliasing. It is therefore possible to image a grating (with the same mean luminance as its surround) on the peripheral retina so that patterned contrast can be detected but the orientation of the grating not resolved. Similarly, aliasing results in the inability to determine the direction of drift of a grating whose frequency is above the Nyquist limit (Anderson and Hess, 1990). In such situations the minimum angle of detection (MAD) is measurably smaller than the MAR. Thibos et al. (1987a) discussed the differences between MAD and MAR. Weymouth had previously advocated that 'it is the density of the ganglion cells…which should be related to the minimal angle of resolution'. Expanding on this Thibos et al. proposed that 'if the retina limits pattern *detection*, then it will be because of the *size* of the largest receptive field in the sequence, presumably the ganglion cells'. This in effect means that MAR is determined by ganglion cell spacing and MAD is determined by ganglion cell receptive field size.

It is noted that, foveally, the phenomenon of aliasing is not ordinarily observable because the optics of the eye remove all spatial frequencies beyond the Nyquist limit of the retina and in effect act as an 'anti-aliasing' filter. Thus, for gratings, MAR and MAD have the same value in the fovea. Snyder et al. (1986) point out that improving optical image quality leads to improved contrast sensitivity but at the potential cost of increased aliasing (a warning in the era of adaptive optics!). Therefore, they argue that optical image quality is a trade-off between the advantage of increased contrast sensitivity and the disadvantage of increased aliasing. Interestingly, Thibos (1989) suggests that the aliasing observable peripherally may not be all bad and that, in survival terms, an aliased percept may be better than none at all!

8.4. Further evidence for sampling limited performance

If the limiting factor for performance on any particular task is purported to be retinal sampling, the task should display some robustness to other factors such as loss of contrast or optical defocus. Thibos et al. (1996) measured detection and resolution performance for sinusoidal gratings of varying contrast in peripheral vision and found that while detection performance declined steadily with decreasing contrast, resolution performance remained optimum until contrast fell to around 10%. At that point detection and resolution performance became equal and declined together. This study indicated that, above 10% contrast, any inability to resolve the grating was not because it was not visible, but because the retinal sampling density was not sufficiently high to veridically represent stimulus orientation. In a similar way, the author (Anderson, 1996b) and Wang et al. (1997) examined the effects of refractive blur on grating detection and resolution in peripheral vision. They found that detection performance fell steadily with increasing defocus, but resolution acuity could tolerate blur up to 3–4 dioptres before performance suffered. These studies provide further evidence for the sampling limited nature of peripheral resolution. However, there is clinical relevance here. A task that is both directly related to retinal sampling density, and at the same time robust to the effects of contrast loss, whether through lens opacity or oblique axis astigmatism, enables more confident separation of optical and neural losses of vision in diseases like glaucoma.

8.5. Psychophysics vs. anatomy

Peripheral grating resolution acuity has strong theoretical links to retinal ganglion cell density and, under normal viewing conditions, the midget (beta) class of ganglion cells, which forms the majority subpopulation. Recent anatomical studies of ganglion cell density and distribution provide comparison with psychophysical measures of resolution acuity at corresponding locations. When MAR (using interference fringes) was plotted against predicted MAR from anatomical counts of human cone and monkey ganglion cell spacings, MAR closely followed the predicted performance from monkey ganglion cell spacing measurements, but was completely different from cone spacing predictions. Further studies measured grating resolution acuity at different eccentricities (Anderson et al., 1991; Anderson et al., 2002) and in different meridians (Anderson et al., 1992) and compared the results to the Nyquist limit predicted from anatomical counts of ganglion cell density in humans at the same locations (Curcio and Allen, 1990). These studies found acuity to be more than twice as high in the nasal retina than the temporal retina providing psychophysical

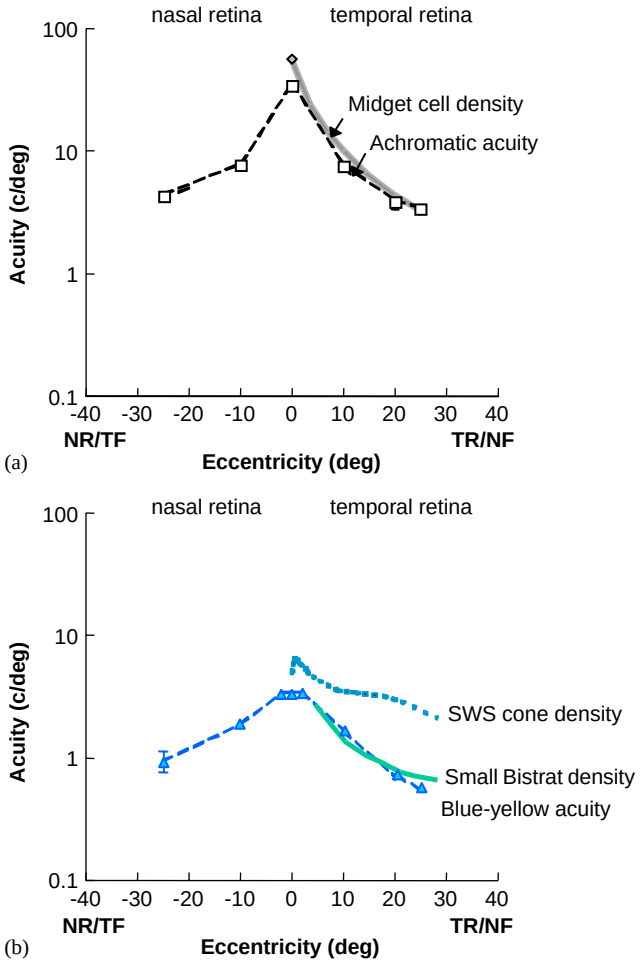

Fig. 5. (a) Resolution acuity vs. eccentricity for achromatic gratings (dashed curve). Resolution performance closely matches expected values from anatomical counts of midget ganglion cell density (solid curve). (b) Resolution acuity vs. eccentricity for blue-yellow gratings (lower dashed curve). Resolution performance closely matches expected values from anatomical counts of small bistratified ganglion cell density (solid curve). Expected resolution based on S-cone density displays different relationship (upper dotted curve).

evidence of a human 'visual streak' similar to that found in other mammals and described by Curcio and Allen in human retina (Curcio and Allen, 1990). The studies also found resolution for achromatic gratings to be lower than the predicted Nyquist based on the total ganglion cell population, but remarkably close to predicted values if only midget ganglion cells are included (Fig. 5a).

8.6. Confirmation of sampling-limited performance

In summary of this section, in order to confirm that any acuity measurement is limited by the sampling density of the underlying retinal ganglion cells, as opposed to the filtering properties of the eye's optics or the ganglion cell receptive field diameter, the following confirmations should be made:

i. the task should be a resolution one (either orientation or drift direction discrimination) and not detection,
ii. if the stimulus has the same mean luminance as its surround, detection performance should be significantly higher than resolution performance,
iii. the presence of aliasing should be observable at higher spatial frequencies,
iv. the resolution threshold should be unaffected by significant contrast reduction,
v. localised resolution measurements should be close to what would be predicted from anatomical studies of ganglion cell density across the retina.

Peripheral resolution acuity thus appears to be a good method of obtaining localised indirect measurements of ganglion cell density in vivo.

9. Resolution perimetry

In order to better tie psychophysical threshold to retinal ganglion cell density, several researchers have in recent years begun to develop different kinds of resolution perimetry where the subject is asked to indicate something more than just the presence of a stimulus of varying contrast. This section will attempt to review the work and the theory behind it.

9.1. The work of Charles Phelps

In 1984, Phelps (Phelps, 1984; Phelps et al., 1984) reported the development of an acuity perimeter based on measures of resolution of interference fringes at different retinal locations. The early reports did not dwell heavily on the theory behind the test, hardly surprising since the limits to peripheral acuity had received little attention up to then, but the test was an intelligent departure from conventional methods. Early results appeared promising but perhaps two things prevented further development. The first was the clumsiness of a procedure based on Maxwellian-view interferometry where careful pupil alignment at every location is essential. The second was undoubtedly the untimely death of Charles Phelps at a young age before the idea of resolution perimetry could be further developed with the aid of computer generated stimuli.

9.2. High-pass resolution perimetry

In 1978, Howland et al. (1978) reported the development of 'high-pass' letter targets which, when viewed foveally, were either invisible or fully resolvable. Since the letters contained no low-frequency components, as they reduced in size the eye's optics quickly removed the remaining high-frequency information, permitting nothing to pass to the retina. These targets, which for the first time afforded equal detection and resolution thresholds for letter stimuli, behave in the fovea in a similar fashion to the grating described above in that they have the same mean luminance as their surround; thus spatial frequencies higher than the resolution limit of the retina do not pass through the optics. High-pass targets were employed in the development of high-pass resolution perimetry (HRP) (Frisen, 1987a, b, 1998) which attempted to measure thresholds that are more closely related to ganglion cell density than conventional perimetric light sensitivity. The assumption was that, since detection and resolution thresholds are the same for such targets, measurements of detection threshold alone (of a high-pass ring) would also provide a measure of ganglion cell sampling density (Frisen, 1987a, b, 1998). However, as with gratings, while detection and resolution thresholds for high-pass ('Vanishing Optotype') targets may be the same in the fovea (Frisen, 1986), they are not the same outside the fovea and aliasing is clearly observable (Anderson and Ennis, 1999) meaning detection acuity for such stimuli does not provide an estimate of ganglion cell spacing or density, but more likely receptive field size (Thibos et al., 1987a). To yield a sampling-limited threshold the patient should distinguish between two or more different high-pass targets (resolution). However, the high-pass nature of the stimuli means that, in order to resolve the high frequencies contained within such a stimulus, it must become very large (Anderson and Ennis, 1999) with a resulting loss of localisation.

9.3. Achromatic resolution acuity in glaucoma

Several studies have measured localised resolution acuity in glaucoma subjects. We measured conventional perimetry thresholds and localised resolution for Tumbling E letters in 15 early glaucoma subjects and examined the correlation between these measures and

optic nerve dimensions using Heidelberg retinal tomography (HRT). We found a significant correlation between neural rim volume and resolution acuity ($r = 0.70$) but not conventional perimetry thresholds ($r = 0.25$)(Fig. 6).

Beirne et al. (2003) measured sinusoidal grating resolution performance at different retinal locations in early glaucoma patients and normals. They found that many retinal areas displaying no significant sensitivity loss by conventional perimetry showed significant localised resolution acuity loss (Fig. 7a). In addition, no retinal location identified as abnormal by conventional perimetry displayed normal resolution values. This study adds significant weight to the argument that many 'normal' areas of a glaucomatous visual field are actually abnormal, having lost large numbers of ganglion cells, even with high contrast stimuli. More recently, Spry et al. (2005) compared the power of various perimetric types, including grating resolution perimetry, to discriminate between normal, glaucoma suspect and early glaucoma subjects. Using ROC analysis, their results found poor discriminatory ability for resolution perimetry based on MD, but significantly improved ability based on PSD, TD and PD. Repeatability was also poor compared to other tests. However, these findings are mostly explainable by two facts. Firstly, the inter-individual variability in absolute ganglion cell numbers is high even in normal eyes (Curcio and Allen, 1990), meaning average resolution values can often be higher in glaucoma patients than normal subjects; the detection of pathologically reduced resolution requires comparison with other areas of the retina and/or monitoring over time. Secondly, and more importantly, their resolution test used as 2-alternative forced choice task with a 2-up/1-down reversal threshold algorithm: this results in a 1-in-4 chance of guessing correctly and enormous threshold variability. The authors acknowledged that their acuity perimetry tests were not optimised in terms of stimulus configuration and threshold algorithm compared to the others, something that is required in order to improve future clinical utility. In addition, the task requires somewhat more concentration than conventional perimetry in that it requests the patient to identify the stimulus orientation and not merely its presence. Nevertheless, resolution acuity perimetry, being sampling limited, offers a more direct link to the density of surviving ganglion cells and, by comparison of resolution using stimuli of different contrast, could shed some light on the proportion of cells which are 'sick' rather than totally dysfunctional at different stages of the disease process.

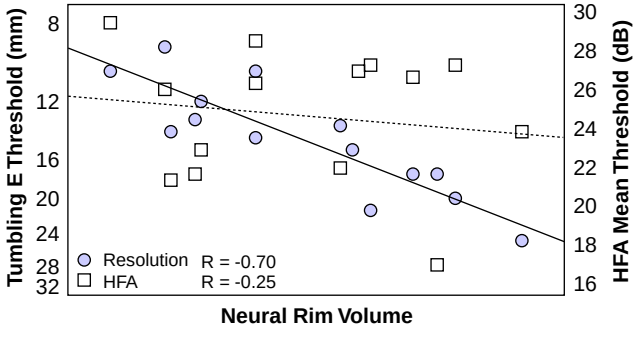

Fig. 6. Resolution acuity (dots) and Humphrey perimetry threshold (squares) vs. neural rim area in early glaucoma.

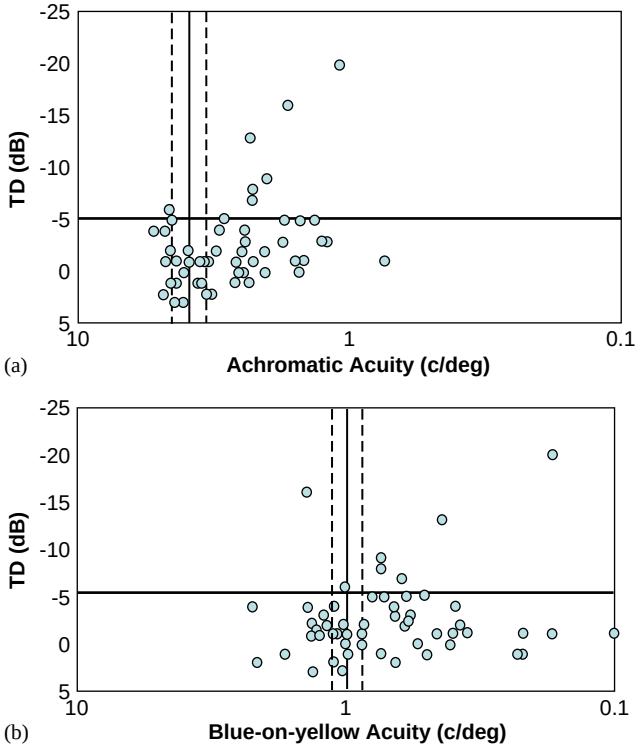

Fig. 7. Localised HFA total defect vs. resolution acuity for (a) achromatic and (b) blue-yellow gratings in early moderate glaucoma. Vertical solid line is mean resolution for normal subjects. Vertical dotted lines represent 95% confidence limits for resolution. Note number of points appearing normal by conventional perimetry which display significantly reduced resolution for both grating types.

9.4. Magno- vs. Parvo-resolution loss

Since peripheral grating resolution was known to be sampling limited, Anderson and O'Brien (1997) measured peripheral resolution for both stationary gratings and gratings which phase-reversed at 30 Hz in a group of early glaucoma patients and age-matched normals. This would yield estimates of responding ganglion cell density for both kinds of stimulus and a comparison of the ratio of the two measures in glaucomatous and normal subjects should provide an indication of selective loss of different responding cell groups. They found that the flicker/non-flicker resolution ratio was significantly lower in the glaucoma subjects and took

this to indicate a selective loss of flicker-sensitive cells, i.e. magnocellular ganglion cells. However, as noted earlier, the response characteristics of the magno- and parcocellular systems to achromatic stimuli are not so different. In addition, later studies of peripheral resolution for both drifting (Anderson et al., 1995) and phase-reversing (Anderson, 1996a; McKendrick and Johnson, 2000) gratings indicated that, while resolution performance remains sampling-limited for higher contrast stimuli up to at least 25–30 Hz, resolution performance at these temporal frequencies is much too high to be limited by the sparse magnocellular ganglion cell subpopulation. It appears that most parvocellular ganglion cells are perfectly capable of responding to temporal frequencies up to 30 Hz and, while there may indeed be a loss of motion sensitive cells in early glaucoma, we can not definitively say these belong to the magnocellular pathway, or even that the magnocellular pathway participates at all in the task. Nevertheless, many studies of motion sensitivity loss in glaucoma continue to assume 'isolation' of the magnocellular pathway by flickering or moving stimuli.

9.5. Limits to chromatic resolution

Many previous studies have determined that achromatic grating resolution acuity was sampling limited outside the fovea. Anderson et al. (1991) found the same for red-green gratings in peripheral vision in that subjects were able to detect such stimuli at spatial frequencies much higher than their resolution limit. Recent studies using S-cone isolating gratings also provide strong evidence for the sampling-limited nature of resolution mediated by the sparse SWS system, not only in the peripheral retina but also in the fovea, using both interferometric (Williams et al., 1983; Metha and Lennie, 2001) and computer generated stimuli (Anderson et al., 2002). In these studies detection acuity for blue-on-yellow gratings was superior to resolution acuity at all locations, and subjects could subjectively observe chromatic aliasing ('splotchiness') of the stimulus percept. In addition, resolution acuity for such SWS isolating gratings is remarkably robust to the effects of optical defocus and simulated age-related lens yellowing (Anderson et al., 2003) indicating that, so long as a certain minimum contrast was available, resolution performance remained optimum and was only constrained by the density of the underlying ganglion cell sampling mosaic. The measured resolution values at each eccentricity closely matched the expected resolution based on anatomical counts of small bistratified ganglion cell density (Anderson et al., 2002) (Fig. 5b), and indicated the potential of such a resolution test to measure small bistratified ganglion cell density in conditions like glaucoma.

9.6. Chromatic vs. achromatic resolution loss in glaucoma

Knowing that resolution for both achromatic and blue-on-yellow gratings is sampling-limited outside the fovea and closely related to the density of the responding ganglion cell population, Beirne et al. (2003) mentioned above, measured resolution performance at different retinal locations using blue-on-yellow as well as achromatic gratings in early glaucoma patients and normals. They found that many areas displaying no significant sensitivity loss by conventional perimetry showed significant resolution loss for both achromatic (Fig. 7a) and chromatic stimuli (Fig. 7b).

However, the chromatic/achromatic resolution ratio was no different between the glaucoma and normal groups indicating no selective loss of one pathway over another. The study briefly discussed the implications of the findings for selective damage to one or other pathway and pointed out that, since contrast of both kind of gratings was high at a cone level, even cells which were 'sick' could still detect the gratings and participate in the resolution task; thus they had no way of knowing if one population is more healthy than another at the time of testing, or what the relative time-course to death might be. Are the reported early losses of SWS in SWAP a result of selectively suppressed S-cone pathway function, perhaps owing to deficient synaptic neurotransmitter release prior to cell death? Could this change in neurotransmitter release and/or cell shrinkage result in a change of perceptive field size in early glaucoma? Clearly much work remains to be done in order to answer these questions.

10. Conclusion

Many new psychophysical tests have been introduced in recent years in order to detect glaucomatous damage at a stage where treatment might be more effective and this goal should remain a priority. These novel tests, in their present form, display differing levels of detectability, repeatability and ease of clinical use. Some may not actually measure what the designers initially claimed they did. This does not mean however that the test is not clinically useful. It could be argued, if it works, who cares what it measures? Nevertheless, in the quest to design a new test of visual function, capable of detecting the earliest losses of visual function caused by glaucoma, or any other ocular condition, care should be taken both in the interpretation of anatomical/physiological findings and the development of good psychophysical theory in order to ask the appropriate subjective questions of the visual system. Sometimes it may be required to return to classical psychophysical studies conducted many years ago by scientists who could not

foresee the relevance of their work to clinicians working in glaucoma decades in the future. Without a return to good basic visual theory the clinical scientific literature runs the risk of becoming very muddy water in which the truth becomes impossible to determine and much public funding is wasted in wild goose chases.

Acknowledgements

I wish to thank the numerous friends and colleagues who have collaborated in much of the work described, in particular, Larry Thibos, Colm O'Brien, Fergal Ennis, Margarita Zlatkova and Raymond Beirne. I especially thank Angel Vassilev for his insightful comments on the manuscript.

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